Original Research

Epidemiology, potential risk factors and outcome of black fungus during COVID-19 pandemic: a concurrent prospective study at a dedicated COVID-19 hospital of North India

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Abstract

Introduction: As the number of COVID-19 patients increased during second wave, a steep rise of patients with mucormycosis was found in all parts of India.

Objectives: To determine the epidemiological factors leading to the rise in fungal infection in patients during COVID-19 pandemic as well as describe the outcome of the disease during next three months after being discharged from the hospital

Methods: It was a concurrent prospective study conducted between 26 June to 25 October 2021 at ESIC Medical College & Hospital, Faridabad, India. Patients positive for mucormycosis and agreed for the study were enrolled. They were interviewed telephonically after recording their consent.

Results: A total of 51 patients were interviewed during our study period. During the follow-up, six patients died within three months of discharge from the hospital. The mean age of patients was 49.6years (SD=6.9 years), with the majority in the age group of 41-60 years. Most (53%) of the patients were males and 30(58.8%) were graduates and above. In the sample, 33 had a recent history of COVID-19 infection, 24 (47%) had been prescribed steroids, 16 (31.3%) had been prescribed oxygen during COVID-19 infection and 33(64.7%) were diabetic. The relationship of potential risk factors with the type of mucormycosis was not found to be statistically significant. Out of the45 patients who survived, 35 were better, three were still on oral anti-fungal treatment and seven patients required reconstructive plastic surgery. A significant association was found between patients who had a history of steroid intake and type of mucormycosis.

Conclusions & Recommendations: Patients admitted to hospital with mucormycosis during the COVID-19 surge mostly had a history of COVID-19 infection, suffering from diabetes or on steroids. Most of the patients survived due to treatment availability (antifungal medicines, surgery or both) and about 15% of them had undergone long debridement surgery leading to severe loss of normal contour of the face and waiting for plastic reconstructive surgery.

Keywords: *steroid, outcome of mucormycosis, diabetes, COVID-19*

Introduction

With the second wave of COVID-19 cases during April 2021, another disease emerged as public health concerned commonly called as 'black fungus or invasive mucormycosis post COVID-19 Mucormycosis is a serious and potentially fatal fungal infection caused by a type of rare, invasive but opportunistic fungal pathogen called Mucoromycetes (1). Though uncommon in immune-competent patients, a rapid upsurge of systemic mucormycosis has been documented in patients suffering from malignancy, uncontrolled diabetes mellitus (DM), persons living with HIV, and indiscriminate use of systemic antimicrobials and other immune-compromised states (2). The classification of mucormycosis is done on the basis of anatomic localisation, such as rhino-orbital-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal and disseminated mucormycosis (3).

Before the pandemic, the load of mucormycosis in India was about 14 cases per 100 000 population, which is one of the highest at the global level (4). However, from May to July 2021, India has reported more than 47000 cases of mucormycosis, and the actual figure is likely to be higher. The crisis was further worsened by an acute scarcity of Amphotericin B, a drug used for the treatment of mucormycosis (5). An epidemiological survey conducted two decades ago suggested that mortality rate of mucormycosis is as high as 54%, if left untreated (6).

There are multiple views regarding the current mucormycosis outbreak in India. The main reason postulated was increased germination of Mucorales in COVID-19 patients. The fertile land provided by pre-existing DM, new onset hyperglycaemia and steroid induced hyperglycaemia accounts for the main reason for the outbreak (7-9). The other factors contributing for germination are low oxygen saturation, metabolic acidosis, high iron level as evidenced by high ferritin, immunosuppression due to SARS-CoV-2 mediated, steroid mediated or pre-existing comorbidities causing decreased phagocytic activities by white blood cells. A few authors also suggest prolonged hospitalization, and increased ventilator use in COVID-19 might have contributed to the increased risk of mucormycosis (10). Indiscriminate use of industrial oxygen and contaminated masks were also thought to be risk factors for the upsurge (10-12).

The present study was undertaken with the aim of determining the patient demographics, risk factors contributing to the disease, presenting symptoms and signs, the role of comorbidities and medications used to treat COVID-19, and the outcomes of management. The information provided by our study can help medical professionals to have a high index of suspicion in the presence of typical symptoms and signs and curtail risk factors associated with mucormycosis as much as possible and also to establish post-COVID-19 follow up protocols.

Methods

We conducted a prospective observational study from June to October 2021 at ESIC Medical College & Hospital, NIT 3 Faridabad, India. Telephonic interviews were conducted with the participants on their preferred timing who fulfilled our inclusion criteria and were willing to give verbal consent on telephone for the study to record their interviews. All consecutive individuals with proven mucormycosis were enrolled during the study period. We defined proven mucormycosis as those individuals with clinically compatible disease and the demonstration of fungi in the tissue (or body fluids) either by direct microscopy (broad ribbon like aseptate hyphae), culture or molecular methods. All participants received treatment at the discretion of the treating physician.

We collected the following information on a standardized case report form: (a) demographic details; (b) clinical features; (c) predisposing factors (DM, glucocorticoid therapy, transplant, malignancy, immunosuppression, and others); (d) co-morbid illnesses (ischaemic heart disease, chronic kidney disease, chronic liver disease,

chronic respiratory illnesses, and others); (e) site of disease (pulmonary, rhino-orbital with or without cranial extension, or others); (f) details of treatment given (antifungal agent, dose and duration of antifungal agent, nature of surgical treatment); and (g) mortality at 90 days.

Data analysis

The data were analysed using the commercial statistical package SPSS (version 20.0) for MS-Windows (IBM Inc., Chicago, IL). The descriptive statistics are presented as frequencies and mean with standard deviation (SD), as appropriate. The categorical variables were compared using Chi-squared test (or Fischer's Exact Test as appropriate). A p-value <0.05 was considered as significant.

Results

During the study period, a total of 58 consecutive mucormycosis cases were diagnosed at our hospital. Seven cases were unavailable on phone for interview. Of the remaining 51 cases, 33 (64.7%) had a past history of COVID-19 infection. The mean age of the entire study population was 49.6years (SD=6.9 years); and 53% were men. Most of the patients (59%) were graduates and above. Most of them were from urban areas (65%). Out of the total patients, 9 (17.6%) had the habit of both smoking and drinking alcohol.

Out of the total 51 patients, majority 33 (64.7%) had a history of COVID-19 infection in the past. It was found to be significantly associated with age group, education and occupation of the participants with their past history of COVID-19 infections (Table 1). Among the patients, 33 (64.5%) were diabetic, 13 (25%) were hypertensive and 6 (12%) were on TB treatment. A significant association was found between patients who had a history of steroid intake and the type of mucormycosis (Table 2).

All 51 mucormycosis patients included in our study were followed up for three months, out of which six participants expired during the course of our study and the remaining 45 patients were interviewed on a regular basis for 3-months. The death rate for mucormycosis patients was calculated as 6/51 x100 (11.7%). Out of the total 51 patients, 35 (68.6 %) were better and leading their near normal life. At the end of the three-month follow-up period, 3 (5.9%) patients were still on oral antifungal drugs and 7 (13.7%) required plastic reconstructive surgery for full recovery from the ailment.

Table 3 shows the association of outcome of mucormycosis in patients at the end of three months with the type of mucormycosis. Out of total 51 patients, 5 (9.8%) were categorized into pulmonary type, 25 (49%) were rhino-orbital type and 21 (41.2%) were rhino-orbito-cerebral type of mucormycosis. The associations of type of mucormycosis with the potential risk factors were not found to be statistically significant.

Discussion

India has witnessed a sudden spike of cases of mucormycosis during the second wave of COVID-19 pandemic. Most of the patients presented to the hospital were thought to be as sequel of COVID-19 infection in which discriminate use of antibiotics, steroids, oxygen, and home remedies for COVID-19 were reported. Mucormycosis is known to be a fungal disease which is mostly found in an individual with pre-existing co-morbid conditions. Age remains an important factor to mention here because with aging the immunity of an individual decreases. Therefore, in our study as well in many other studies (10, 13), it has been found that most elders suffered from this disease and had the need to be admitted to a health care institution.

The majority of patients suffering from mucormycosis in our study were giving a past history of COVID-19 infection. It has been postulated by scientists that COVID-19 infection causes endothelialitis, endothelial damage, thrombosis, lymphopenia and reduction in $CD4^+$ and CD8-cell counts, therefore leading to opportunistic

infections including fungal infection. Similar findings have been noted in the meta-analysis done by Singh et al. (2011) (10) and the study done by Mishra et al. (2021) (14). In our study, it has been found that 65% of the patients admitted to our hospital with mucormycosis were suffering from DM too. Out of the total, three patients were unaware of their blood sugar level. This finding is consistent with similar studies done in India during or before the COVID-19 wave, in which it was found that most of the patients presented with mucormycosis were either already diagnosed or diagnosed as diabetics in the course of treatment of mucormycosis (10, 15-16). The patients with DM have decreased immunity which left these patients susceptible for any infection including mucormycosis (15). There is an alteration of phagocytic pathways in patients with DM. Therefore, macrophages are not able to engulf Mucorales spores and free spores tend to swell, and they often turn into buds around the blood vessels. Due to impairment of poly morpho nuclear cells in diabetics, it is also difficult to prevent the spread of Mucorales resulting in extensive invasion of tissues and blood vessels. Similar findings of diabetic patients getting COVID-19 infection leading to mucormycosis had been presented by other researchers too (8, 17-20). Out of 51 patients, 33were giving a recent history of COVID-19 infection. The association of COVID-19 infection with type of mucormycosis was also found to be statistically significant. The increase in germination of Mucorales has been found to be the main reason for increased incidence in COVID-19 patients. The same finding has been found in many studies done during COVID-19 surge in India and outside India (7-9, 21-22).

The association of the intake of steroids with the mucormycosis was also found to be statistically significant in our study. Similar findings were observed in meta-analysis done by Iyer Mahalaxmi et al. (2021) (23). The large-scale use of steroids during COVID-19 upsurge must have further decreased the immunity leading to secondary infection including fungal infection (22).

Out of 51 patients who were enrolled in our study, six patients expired during the follow-up, while 35 (68.6%) were doing well and had only mild symptoms but they were not on any regular medication for mucormycosis. Most of the patients were feeling better after being treated either by a course of antifungal or combination of antifungal medicines with surgical procedure. Prior to the COVID-19 era, mucormycosis was notorious for its poor prognosis, especially with delayed treatment, which might result in a greater fatality rate. Mortality and morbidity have been identified to be associated with the invasiveness of the disease (24). The systemic review (25). Jafar et al. (23) has come up with better outcome of cases with mucormycosis due to early intravenous antifungal and surgical intervention.

Among the limitations of the study, few of the severely sick patients could not be interviewed, and therefore the outcome of those suffering from severe forms of mucormycosis could not be assessed. During our study, the exact cause of death of six patients due to mucormycosis could not be verified.

Conclusions & Recommendations

The surge of invasive fungal infection during the second wave of COVID-19 pandemic led to perplexity among health care professions and health administrators. History of recent COVID-19 infection with co-morbidities like DM and steroid intake was the most common feature found in our study participants. Although the majority of patients survived in our study, it could have been due to the availability of treatment (antifungal medicines, surgery or both), still some patients died during the initial phase of the disease. A few patients had to undergo surgical debridement of the necrotic area which included resection of the affected part, thereby waiting for plastic reconstructive surgery increasing the burden of the disease and long-term morbidity .

The information provided by our study can help medical professionals to have a high index of suspicion in the presence of typical symptoms and signs and curtail risk factors associated with mucormycosis as much as possible and also establish post-COVID-19 follow up protocols.

Table 1: Association of demographic profile of mucormycosis patients with past history of COVID-19 infection (N=51)

Variables	Post COVID-19		Total	p value
	No	Yes		
Age group (in years)				
20 – 40	1 (5.6%)	11 (33.3%)	12	
41 – 60	10 (55.6%)	20 (60.6%)	30	**0.003**
61 – 80	7 (38.9%)	1 (3.0%)	8	
>80	0 (0.0%)	1 (3.0%)	1	
Gender				
Female	11 (61.1%)	13 (39.4%)	24	0.14
Male	7 (38.9%)	20 (60.6%)	27	
Education				
Illiterate	2 (11.1%)	14 (42.4%)	16	
Secondary	15 (83.3%)	4 (12.1%)	19	**0.0001**
Graduate & above	1 (5.6%)	15 (45.5%)	16	
Occupation				
Unemployed/Housewife	12 (66.7%)	8 (24.2%)	20	
Skilled worker	1 (5.6%)	15 (45.5%)	16	**0.004**
Professional	5 (27.8%)	10 (30.3%)	15	
Area				
Rural	6 (33.3%)	12 (36.4%)	18	0.83
Urban	12 (66.7%)	21 (63.6%)	33	
Marital status				
Married	17 (94.4%)	25 (75.8%)	42	0.94
Unmarried	1 (5.6%)	8 (24.2%)	9	
Habits				
Alcoholic	2 (11.1%)	5 (15.2%)	7	0.69
Non-alcoholic	16 (88.9%)	28 (84.8%)	44	
Smoker	2 (11.1%)	8 (24.2%)	10	0.26
Non-smoker	16 (88.9%)	25 (75.7%)	41	
Both alcoholic & smoker	4 (22.2%)	5 (15.2%)	9	0.53
Non-smoker/ alcoholic	14 (77.8%)	28 (84.8%)	42	

Table 2: Association of potential risk factors with type of mucormycosis (N=51)

Risk factors	Type of mucormycosis			Total	p value*
	Pulmonary	Rhino-orbital	Rhino-orbito-cerebral		
Diabetes	5 (15.2%)	13 (39.4%)	15 (45.5%)	33	0.86
Hypertension	1 (7.7%)	6 (46.2%)	6 (46.2%)	13	0.89
TB medication	0 (0.0%)	5 (83.3%)	1 (16.7%)	6	0.19
Hypothyroidism	1 (16.7%)	4 (66.7%)	1 (16.7%)	6	0.42
Cardiovascular	0 (0.0%)	6 (75.0%)	2 (25.0%)	8	0.24
Covid infection	5 (15.2%)	16 (48.5%)	12 (36.4%)	33	0.19
Steroids taken	6 (25.0%)	10 (41.7%)	8 (33.3%)	24	**0.03**
Oxygen therapy	2 (12.5%)	9 (56.3%)	5 (31.3%)	16	0.61
Home remedy used for COVID-19	5 (14.3%)	17 (48.6%)	13 (37.1%)	35	0.26

* Fisher's Exact Test

Table 3: Association of outcomes at the end of three months of patients with type of mucormycosis (N=51)

Outcomes	Type of mucormycosis			Total	p value
	Pulmonary	Rhino- orbital	Rhino-orbito-cerebral		
Better	4 (80.0%)	16 (64.0%)	15 (71.4%)	35 (68.6%)	0.79
On antifungal medicines	0 (0.0%)	2 (8.0%)	1 (4.8%)	3 (5.9%)	
Needed plastic surgery	0 (0.0%)	5 (20.0%)	2 (9.5%)	7 (13.7%)	
Death	1 (20.0%)	2 (8.0%)	3 (14.3%)	6 (11.8%)	
Total	**5 (100.0%)**	**25 (100.0%)**	**21 (100.0%)**	**51 (100.0%)**	

Public Health Implications

- The information provided by our study can help medical professionals to have a high index of suspicion in the presence of typical symptoms and signs and curtail risk factors associated with mucormycosis as much as possible and to establish post-COVID-19 follow up protocols.

Author Declarations

Competing interests: The authors declare that they have no competing interests.

Ethics approval and consent to participate: Ethics clearance was granted by the Ethics Review Committee of ESIC Medical College & Hospital, Faridabad, India (134 X/11/13/2021-IEC/15). Informed verbal consent was obtained from each participant prior to data collection.

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Author contributions: MK participated in concept,

developing tool and writing the research article. SS, PG and RPD participated in data collection, taking interview and consent for the study. JS contributed to the valuable follow-up with the patients as ENT specialist. LP worked as statistician and contributed to the data analysis.

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